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OPTICAL ROTATORY DISPERSION AND ABSOLUTE CONFIGURATION—IV

α-SUBSTITUTED ALCOHOLS AND THEIR DERIVATIVES[1]

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Abstract—Optical rotatory dispersion measurements on α-hydroxy acids, α-substituted alcohols, and their derivatives indicate that a knowledge of the dispersion curve between 200 and 225 mμ permits the direct assignment of the absolute configuration of these compounds. In this way the configurational identity of D-glyceric acid, D-serine, D-lactic acid and D-alanine with D-glyceraldehyde has been confirmed, and compounds derived from, or related to, α-substituted alcohols may thus be correlated with D-glyceraldehyde.

IT WAS shown earlier[2,3] that a knowledge of the direction of the optical rotatory dispersion curve between 200 and 225 mμ makes possible the direct assignment of absolute configuration for a variety of amines possessing a single α-asymmetric centre, including α-amino acids and their derivatives, and pyrrolidine, piperidine, and tetrahydroisoquinoline alkaloids. In the case of amino compounds containing a chromophore absorbing above 200 mμ, anomalous dispersion curves were obtained, while for bases lacking such a chromophore, the observed partial rotation was associated with the known[4] absorption maxima in the 190–200 mμ region ascribed to excitation of the non-bonding electrons of nitrogen.

In view of the importance of configurational relationships between the α-amino acids, α-hydroxy acids, and glyceraldehyde, the validity of extending this method of direct assignment of absolute configuration to these latter compounds, and to α-substituted alcohols (I, $R'' = H$) and esters (I, $R'' =$ acyl) in general, was examined.

In the case of α-hydroxy acids, as in the related α-amino acids,[2] the determination of absolute configuration by the use of anomalous rotatory dispersion measurements was not feasible until recently. Only plain dispersion curves could be obtained in the hitherto accessible wavelength range,[5] and Cotton effects could only be achieved by the use of xanthate derivatives of these compounds.[6] Improved instrumentation is now available, and Jennings and Klyne[7] recently reported Cotton effects at about 225 mμ for 2-hydroxyoctanoic and 3-hydroxynonanoic acids, but no details or curves

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[1] Supported by research grant HE-5881 from the National Institutes of Health, U.S. Public Health Service.

[2] J. C. Craig and S. K. Roy, *Tetrahedron* **21**, 391 (1965).

[3] J. C. Craig and S. K. Roy, *Tetrahedron* **21**, 401 (1965).

[4a] E. Tannenbaum, E. M. Coffin, and A. J. Harrison, *J. Chem. Phys.* **21**, 311 (1953); [b] L. W. Pickett, M. E. Corning, G. M. Wieder, D. A. Semenov, and J. M. Buckley, *J. Amer. Chem. Soc.* **75**, 1618 (1953).

[5] P. Karrer and W. Kaase, *Helv. Chim. Acta* **2**, 436 (1919).

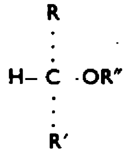
[6] B. Sjoberg, A. Fredga, and C. Djerassi, *J. Amer. Chem. Soc.* **81**, 5002 (1959).

[7] J. P. Jennings and W. Klyne, *Biochem. J.* **86**, 12P (1963).

were given. Since our work was completed, the publication of Dirkx and Sixma[8] appeared, in which positive Cotton effects are reported between 222 and 231 mμ for 5 L-α-hydroxy acids in hydrochloric acid solution, and dispersion curves are given extending down to between 217 and 228 mμ.

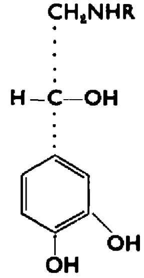
We now wish to record measurements of the anomalous rotatory dispersion of a number of α-substituted hydroxy compounds in the critical 200 to 225 mμ region, to examine the assignment of absolute configuration directly from the dispersion curve. Spectra were generally examined in 95% ethanol and, as in previous cases,[2,3] the curves of both enantiomers were recorded whenever possible, to ensure complete validity for the conclusions reached, regardless of rising end-absorption by the solvent and of scattered light in the 200 to 220 mμ region.

L-(+)-Lactic and L-(+)-mandelic acid have been correlated with L-(+)-alanine and L-(−)-β-phenylalanine,[9] and also with L-(−)-tartaric and L-(−)-malic acid.[9] The dispersion curves of both enantiomers of these hydroxy-acids are recorded in Fig. 1. Our results are reported here only insofar as they are additional to, or differ from, those of Dirkx and Sixma.[8] Our curves extend to 203 mμ, except in the case of mandelic acid where intense end-absorption did not permit valid readings below 219 mμ,



$$\begin{array}{c} R \\ \vdots \\ H-C\cdot OR'' \\ \vdots \\ R' \end{array}$$

(I)



IIa R = Me

IIb R = H

Since the measurements of Dirkx and Sixma terminated at between 217 and 228 mμ, these authors did not observe that the ORD curves of the L-series reached zero rotation at lower wavelengths, and thereafter descended steeply to large and hitherto unreported negative values (−2000 to −16,000°) of the specific rotation, in exact analogy with the previously reported[2] corresponding L-amino acids of identical configuration.[10]

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[8] I. P. Dirkx and F. L. J. Sixma, *Rec. Trav. Chim.* **83**, 522 (1964).

[9a] J. A. Mills and W. Klyne *in* W. Klyne, *Progress in Stereochemistry* Vol. 1; p. 177. Academic Press, New York (1954); [b] E. L. Eliel, *Stereochemistry of Carbon Compounds* p. 91. McGraw-Hill, New York (1962).

[10] It should be pointed out here that while the excellent Cahn–Ingold–Prelog convention[11a] provides a superior method of describing the absolute configuration of compounds, it cannot be used for configurational correlation, since the symbolism R or S may be reversed on substitution on or near the chiral centre, due to the operation of the sequence rule.[11b]

[11a] R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia* **12**, 81 (1956); [b] R. S. Cahn, *J. Chem. Education* **41**, 116 (1964).

It is interesting that (+)-tartaric acid (for an excellent review of tartaric acid nomenclature,[12a]) is apparently configurationally identical (Fig. 1) with D-(−)-mandelic, D-(−)-lactic, and D-(+)-malic acids, and also (Fig. 4; see below) with both D-(+)-serine and D-(−)-glyceric acid. This is in full agreement with Freudenberg's correlation[12b] of carbon 2 of (+)-tartaric acid with D-glyceraldehyde, through D-(+)-malic and D-(−)-glyceric acids, and suggests that tartaric acid is correctly written according to the Fischer convention, i.e. based upon the *lowest-numbered* asymmetric centre, which is the α-carbon, counting from the top. The conversion of D-glyceraldehyde into carbon 3 of (−)-tartaric acid[12c] does not alter this conclusion, since it is known that configuration cannot be assigned on the basis of the compound from which it is derived,[13] and the (−)-tartaric acid obtained in this way would be designated as L when based on the *lowest-numbered* asymmetric centre, i.e. carbon 2, and would be configurationally identical with L-(−)-serine, as shown in Figs. 1 and 4, since it is described according to the same (Fischer) convention.

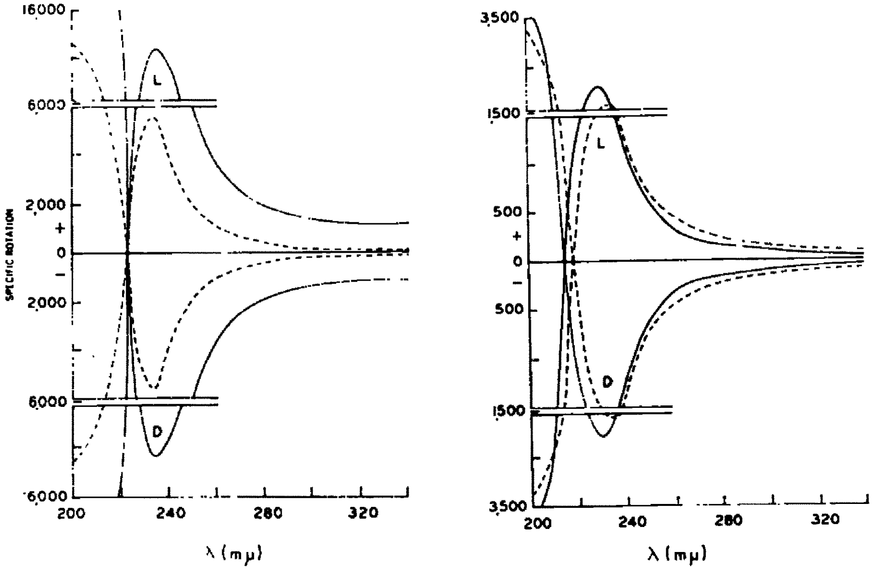

FIG. 1. Rotatory Dispersion Curves
(left) Mandelic acid (———) and tartaric acid (- - - -)
(right) Lactic acid (———) and malic acid (- - - -).

Two biologically significant natural hydroxy compounds containing a phenyl chromophore are (−)-adrenaline (epinephrine; IIa) and the closely related (−)-noradrenaline (arterenol; IIb). The UV spectra of their hydrochlorides show maxima at 282 and 226 mμ, with strong end-absorption below 216 mμ. Their dispersion curves (Fig. 2) have two Cotton effects, corresponding to the UV maxima, superimposed on a strong positive background. Below 225 mμ, the curves ascend steeply like that of D-mandelic acid. The assignment of the D-configuration to both (−)-adrenaline and (−)-noradrenaline is in accord with the chemical transformations[14]

[12a] J. N. Baxter, *J. Chem. Education* **41**, 619 (1964); [b] K. Freudenberg, *Ber. Dtsch. Chem. Ges.* **47**, 2027 (1914); [c] A. Wohl and F. Momber, *Ibid.* **50**, 455 (1917).

[13] Ref. 9*b*, p. 89.

[14] P. Pratesi, A. LaManna, A. Campiglio, and V. Ghislandi, *J. Chem. Soc.* 2069 (1958).

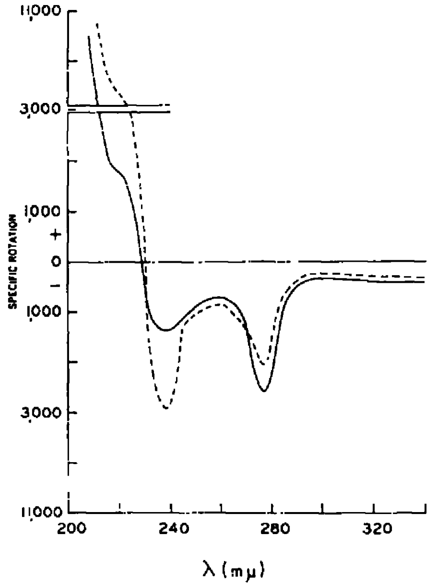

Fig. 2. Rotatory Dispersion Curves of D-(−)-Adrenaline (———) and D-(−)-Noradrenaline (- - - -).

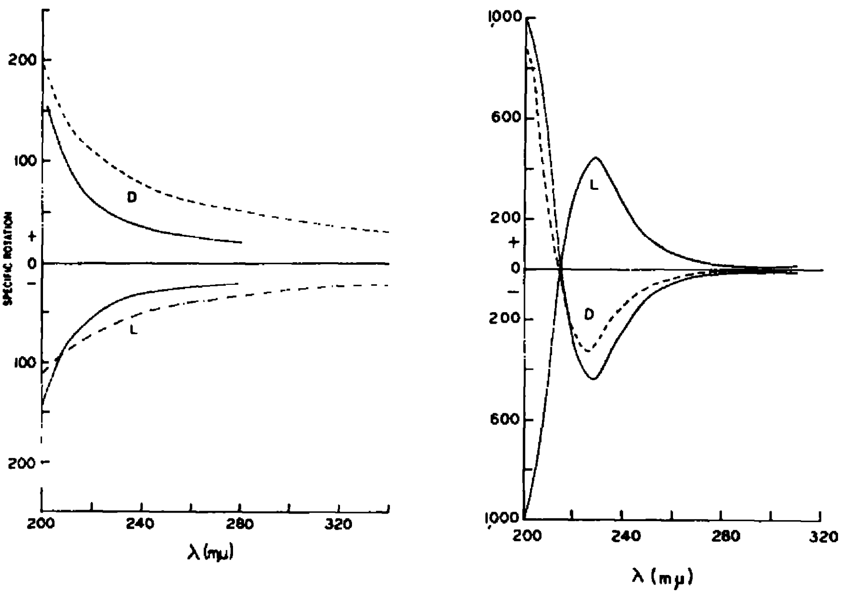

Fig. 3. Rotatory Dispersion Curves
(left) Octanol-2 (———), D-(+)-heptanol-2 (- - - -), and L-(−)-heptanol-3 (- . - . - .)
(right) Octanol-2 acetate (———) and D-(+)-heptanol-2 acetate (- - - -).

correlating the former with D-(−)-mandelic acid, and with the biological conversion of IIb into IIa,[15] and is further evidence against the previous conclusions[16] indicating these compounds to belong to the L-series.

It was of interest to examine alcohols lacking a chromophore other than the hydroxyl group. The configurations of D-(+)- and L-(−)-octanol-2, D-(+)-heptanol-2, and L-(−)-heptanol-3 are known from established chemical relationships[17] and these compounds exhibit plain dispersion curves (Fig. 3) showing the expected steep ascent (D-series) or descent (L-series) below 225 mμ. Saturated alcohols, like the related aliphatic and heterocyclic amines,[3] show only rising end-absorption in the UV, so that the observed rotatory dispersion properties below 225 mμ must be ascribed to a partial rotation associated with the known[18] absorption maxima of alcohols in the 180–185 mμ region, caused by excitation of the non-bonding electrons of oxygen.

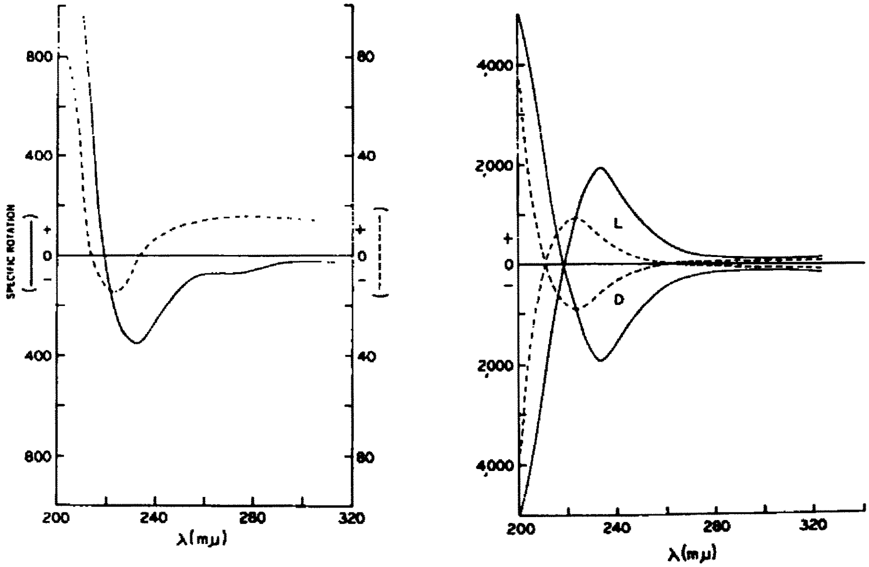

FIG. 4. Rotatory Dispersion Curves
(left) D-(−)-Glyceric acid (———) and Strontium D-(+)-Glycerate (- - - -)
(right) Serine (- - - -) and Serine hydrochloride (———).

Acetylation of heptanol-2 or octanol-2 with acetic anhydride in pyridine produces esters with retention of configuration,[19] as shown by their dispersion curves (Fig. 3) which exhibit a Cotton effect with a peak or trough at about 225 mμ. These compounds possess UV spectra showing only end-absorption, with a shoulder at 226 mμ.

D-(+)-Glyceraldehyde is the standard substance to which all other optically active compounds are referred if possible, and its configuration has been correlated with those of D-(−)-lactic acid, D-(+)-serine, and D-(−)-alanine.[9] While D-glyceraldehyde is unstable and difficult to isolate or purify, and can exist in solution as a

[15a] E. Bülbring, *Brit. J. Pharmacol.* **4**, 234 (1949); [b] E. Bülbring and J. H. Burn, *Ibid.* 245 (1949).

[16] C. E. Dalgliesh, *J. Chem. Soc.* 3323 (1953).

[17] Ref. 9, p. 205.

[18] A. J. Harrison, B. J. Cederholm, and M. A. Terwilliger, *J. Chem. Phys.* **30**, 355 (1959).

[19a] R. H. Pickard and J. Kenyon, *J. Chem. Soc.* **105**, 830 (1914); [b] E. D. Hughes, C. K. Ingold and S. Masterman, *Ibid.* 840 (1939).

mixture of isomeric and polymeric materials, including hydrates and both intra- and intermolecular hemiacetals, the configurationally identical D-glyceric acid can be easily prepared either from dilute solutions of the aldehyde[20] or from any α-methyl-D-hexopyranoside or furanoside.[21]

Oxidation of the D-(+)-aldehyde (the identity of which was confirmed by the preparation of the dimedone derivative, which had the published physical properties[22]) by a modification of the published method[20] gave the stable D-(−)-glyceric acid, isolated as the D-(+)-strontium salt. The dispersion curves (Fig. 4) of both the salt and the acid agree wholly with those of its nitrogen analogue, D-(+)-serine, in neutral and in acidic solution respectively (Fig. 4) down to 200 mμ. The ORD curve of L-serine, in hydrochloric acid solution, was reported by Dirkx and Sixma[8] down to about 210 mμ, and our results for this isomer agree with theirs.

It would therefore appear that in all hydroxy compounds so far examined, in which the hydroxyl group is attached to a single asymmetric centre, the absolute configuration of this centre may be deduced from the direction of the dispersion curve between 200 and 225 mμ, as in the case of the corresponding nitrogen compounds.[2,3] The presence of a chromophore absorbing above 200 mμ is not required, and the results here presented thus permit the direct configurational correlation of D-glyceric and D-lactic acids with D-serine and D-alanine, from an inspection of the ORD curves between 200 and 225 mμ. If further work along these lines confirms their general applicability, they are expected to be of value in making possible the assignment of absolute configuration for a variety of α-asymmetric amines, alcohols, amino acids and hydroxy acids.

EXPERIMENTAL

Rotatory dispersion curves were measured with a Bendix Model 460-C spectropolarimeter using 1 mm or 1 cm cells (c 0·1 to 10·0 in 95% EtOH) at 25°, and were reproducible to within 5%. Rotations are given below only for (1) the highest and lowest wavelengths measured, (2) peaks and troughs. Since measurements taken for enantiomeric pairs agreed within 5%, only one isomer is described.

L-(+)-*Lactic acid.* $[\alpha]_D$ 5·2° (c, 10·5 in 0·1 N HCl). R.D. (c, 0·195 in 95% ethanolic 0·1 N HCl) $[\alpha]_{333}$ 61·2°, $[\alpha]_{229}$ 2047° (peak), $[\alpha]_{204}$ −3415°.

L-(−)-*Malic acid.* $[\alpha]_D$ −2·3° (c, 8·5 in H_2O). R.D. (c, 0·520 in 95% EtOH) $[\alpha]_{333}$ 107°, $[\alpha]_{233\cdot5}$ 1580° (peak), $[\alpha]_{204}$ --2660°.

L-(+)-*Mandelic acid.* $[\alpha]_D$ 155° (c, 2·5 in H_2O). R.D. (c, 0·105 in EtOH) $[\alpha]_{333}$ 1030°, $[\alpha]_{236\cdot5}$ 14,640°, $[\alpha]_{219}$ −16,500°.

L-(−)-*Tartaric acid.* $[\alpha]_D$ −12° (c, 10 in H_2O). R.D. (c, 0·422 in EtOH) $[\alpha]_{333}$ 113·6°, $[\alpha]_{232\cdot5}$ 5443°, $[\alpha]_{204}$ −14,270°.

D-(−)-*Adrenaline.* $[\alpha]_D$ −51° (c, 1·0 in 0·1 N HCl). UV absorption: λ_{max} 226 and 282 mμ, log ε 3·81 and 3·59 in 95% ethanolic 0·1 N HCl. R.D. (c, 0·115 in 95% ethanolic 0·1 N HCl) $[\alpha]_{333}$ −392°, $[\alpha]_{276\cdot5}$ −2570° (trough), $[\alpha]_{260}$ −755° (peak), $[\alpha]_{238}$ −1316° (trough), $[\alpha]_{217}$ 1974° (shoulder), $[\alpha]_{208}$ 8752°.

D-(−)-*Noradrenaline.* $[\alpha]_D$ −40° (c, 5·0 in 0·1 N HCl). R.D. (c, 0·09 in 95% ethanolic 0·1 N HCl) $[\alpha]_{333}$ −333°, $[\alpha]_{276\cdot5}$ −2055° (trough), $[\alpha]_{260}$ −945° (peak), $[\alpha]_{238}$ 2955° (shoulder), $[\alpha]_{210\cdot5}$ 10,460°.

L-(−)-*Octan-2-ol.* $[\alpha]_D$ - 9·2° (c, 5·5 in EtOH). R.D. (c, 1·44 in EtOH) $[\alpha]_{330}$ −19·5°, $[\alpha]_{200}$ −156·0°.

D-(+)-*Heptan-2-ol.* $[\alpha]_D$ 7·8° (c, 12·0 in EtOH). R.D. (c, 1·70 in EtOH) $[\alpha]_{333}$ 33·0°, $[\alpha]_{200}$ 191·0°.

[20a] E. Baer, J. M. Grosheintz, and H. O. L. Fischer, *J. Amer. Chem. Soc.* **61**, 2607 (1939); [b] E. L. Jackson and C. S. Hudson, *Ibid.* **62**, 958 (1940).

[21] E. L. Jackson and C. S. Hudson, *J. Amer. Chem. Soc.* **58**, 378 (1936); **61**, 1530 (1939).

[22] A. S. Perlin *in* R. L. Whistler and M. L. Wolfrom, *Methods in Carbohydrate Chemistry* Vol. I; p. 61. Academic Press, New York (1962).

L-(−)-*Heptan-3-ol.* $[\alpha]_D$ − 5·0° (*c*, 12·0 in EtOH). R.D. (*c*, 1·71 in EtOH) $[\alpha]_{333}$ −22·0°, $[\alpha]_{302}$ −107·5°.

D-(+)-2-*Octyl Acetate.* $[\alpha]_D$ 6·5° (*c*, 5·3 in EtOH). R.D. (*c*, 1·26 in EtOH) $[\alpha]_{320}$ 0°, $[\alpha]_{227}$ −444·5° (trough), $[\alpha]_{200}$ 985°.

D-(+)-2-*Heptyl acetate.* $[\alpha]_D$ 5·5° (*c*, 10·0 in EtOH). R.D. (*c*, 0·85 in EtOH) $[\alpha]_{323}$ 4·0°, $[\alpha]_{225 \cdot 5}$ −337·5° (trough), $[\alpha]_{200}$ 860°.

D-(+)-*Glyceraldehyde dimedone.* This had m.p. 197–198° and $[\alpha]_D$ 204° (*c*, 0·5 in EtOH). [Lit.[22] m.p. 196–198° and $[\alpha]_D$ 210° (*c*, 0·6 in EtOH).] UV spectrum: λ_{max} 269·5 mμ (log ε 3·39) with end-absorption below 220 mμ.

D-(+)-*Strontium glycerate.* This was obtained as microcrystals of a tetrahydrate which lost water at 135–140° but did not melt up to 250°. (Found: C, 19·44; H, 4·87. Calc. for $C_6H_{10}O_8Sr + 4H_2O$: C, 19·26; H, 4·75%), $[\alpha]_D$ 14·1° (*c*, 4·5 in water). The compound has been reported[20b] as a dihydrate, m.p. 136–137°, $[\alpha]_D$ 15·2° (*c*, 0·5 in H_2O). R.D. (*c*, 0·68 in H_2O): $[\alpha]_{300}$ 14·3°, $[\alpha]_{224}$ −14·7° (trough), $[\alpha]_{202 \cdot 5}$ 80·0°.

D-(−)-*Glyceric acid.* Generated by addition of HCl to a solution of the strontium salt, this had $[\alpha]_D$ −3·1° (*c*, 4·5 in 0·1 N HCl). [Lit.[20a] gives $[\alpha]_D$ −3·0° (*c*, 1·1 in H_2O) for the acid.] R.D. (*c*, 10·1 in 0·1 N HCl) $[\alpha]_{312 \cdot 5}$ −10·4°, $[\alpha]_{232 \cdot 5}$ − 347·5° (trough) $[\alpha]_{209 \cdot 5}$ 978°.

D-(+)-*Serine.* R.D. (*c*, 0·30 in EtOH): $[\alpha]_{322 \cdot 5}$ 64·5°, $[\alpha]_{225}$ −894° (trough), $[\alpha]_{200}$ 3685°. The hydrochloride had $[\alpha]_D$ −14·0° (*c*, 9·0 in N HCl), and R.D. (*c*, 0·30 in 95% ethanolic 0·1 N HCl) $[\alpha]_{322 \cdot 5}$ −53·7°, $[\alpha]_{234}$ −1926° (trough), $[\alpha]_{200}$ 4925°.